REMARKS

Claims 1, 7, 31-40 and 42-45 were previously canceled from the case. Claims 2, 24 and 41 are amended herein.

Claims 2 and 41 have been amended to recite, in step (i) that the step is accomplished "without an intervening step of culturing cells from the sample." Verbatim support for this language can be found at page 13, lines 12-13 of the specification as filed.

Claim 24 was inadvertently omitted from the list of claims in Applicants' previous response. The claims also amended herein to recite "inserting the isolated genomic DNA into a BAC or PAC vector," thus paralleling the language of Claim 22. Support for this language can be found at page 19, lines 17-19, of the specification as filed.

Claims 2-6, 8-30, 41 and 46-48 remain in the case.

Favorable reconsideration is respectfully requested.

Rejection of Claim 2 under 35 U.S.C. §112, First Paragraph (Written Description):

Applicants note a slight discrepancy in the presentation of the rejection. At page 2 of the Final Office Action, only Claim 2 is made subject to this rejection. However, at page 3 of the Final Office Action, "Claims 2 and 33" are made subject to this rejection. Applicants respectfully note that Claim 33 was previously canceled from the case. Applicants' undersigned counsel has thus assumed that only Claim 2 is subject to this rejection. If this is not that case, clarification of the rejection is requested.

As applied to claim 2, Applicants respectfully traverse this rejection because the specification as filed provides an ample written description of the **method** that is recited in the claims. As is clearly indicated by the Office's remarks at the top of page 4 of the Final Office Action, the Office is improperly rejecting the present **method** claims based on a misplaced insistence that all of the compounds that can be detected by the method must be revealed in the description. Applicants respectfully note that it is the language of the claims that drives the written description requirement. Applicants need not describe in any detail information that is not relevant to the positive language of the claims. "The purpose of the written description requirement is to prevent applicants from later asserting that they invented that

which they did not." *Inverness Medical Switzerland GmbH v. Acon Laboratories Inc.,* 367 F.Supp.2d. 182, D. Mass., April 29, 2005. Here, Claim 2 is directed to a **method for detecting** a compound produced by transformed host cell, a compound that is not produced by the **un**-transformed host cell. Applicants **are not** claiming any compounds whatsoever. For this reason, Applicants respectfully submit that this rejection is clearly improper.

Regarding the claimed method, Applicants submit that the application as filed clearly describes, in great detail, the invention that is positively recited in the claims.. For example, the passage at pages 13-19 of the specification contains an extensive discussion on sources for suitable microbial DNA to be used in the claimed method. Pages 15 and 16 in particular discuss several different methods for extracting the DNA from an environmental sample: (i) direct extraction by treating with an extraction buffer, a protease, and SDS, without isolating the organisms in the sample (page 15, first full paragraph); (ii) isolating the microbes in the sample and then extracting the DNA (page 15, second full paragraph); (iii) lysing the microbes by multiple freeze-thaw cycles and then extracting the DNA (page 15, fourth full paragraph); (iv) digesting the cells walls of the microbes with lyticase, followed by DNA extraction (page 15, last paragraph); (v) embedding the microbes in agarose plugs or beads, followed by extracting the DNA (page 16, first full paragraph); and (vi) flow cytometry followed by DNA extraction from the selected cells (page 16, third full paragraph. In short, the specification as filed provides no less than six different approaches to isolating the DNA that is to be used in the claimed method.

Page 17 of the specification as filed contains a description of how to size-fractionate the DNA once it has been isolated. Specifically mentioned as illustrative approaches are pulsed-field gel electrophoresis (PFGE, page 17, third full paragraph) and flow cytometry-based techniques (page 17, fourth full paragraph). Both passages include citations to the relevant scientific literature.

The last paragraph of page 18 of the specification as filed notes that users can get an estimate of the phylogenetic diversity of the isolated nucleic acids by screening the isolated nucleic acids for tRNA sequences that are specific for any given phyla of organims.

At page 19, to the top of page 24, the specification contains a truly extensive discussion of a host of different vectors that can be used in the claimed method, including viral vectors, phage, plasmids, phagemids, cosmids, phosmids, BACs, bacteriophage P1, P1-based artificial chromosomes (PACs), YACs, yeast plasmids, etc. See page 19, second full paragraph. The passage spanning pages 19 to 24 of the specification is extensively documented with references to the relevant scientific literature. Use of the pBeloBAC11 vector is described in great detail (as an exemplary vector) in the passage starting at page 21, second full paragraph.

More notable still is the full, complete, step-by-step example on how to prepare BAC DNA, spanning page 24, second paragraph, to the middle of page 28 of the specification. This passage explicitly addresses, in thorough detail, how to prepare the BAC vector DNA (pages 24-25); how to prepare the source DNA, how to ligate the source DNA into the BAC, and how to electroporate the BAC vector into a suitable host cell (middle of page 25 to the top of page 27); and how to purify the cloned BAC DNA using mini-preps (middle of page 27 to the middle of page 28.

Starting at the last paragraph of page 28 of the application as filed, the specification describes several host cells that can be used in the claimed method. See in particular the list of suitable prokaryotic host cells presented at page 29, second full paragraph.

Starting at the final paragraph at page 29, and extending all the way to the top of page 39, the specification contains a very detailed description of the various detection techniques that can be used in the claimed method. Included in the description are direct chemical and photochemical techniques, characterization of fractionated media, and phenotypic changes in the host cell. Screening for GTPase activity is explicitly described as one detection method (bottom of page 31), as is screening fo the MAP kinas pathway (page 32, fifth full paragraph). Fluorgenic detection methods are described in the large paragraph at the top of page 33. Detection using reporter genes is described starting at page 34, first full paragraph. A number of other detection techniques are also described (along with relevant references to the scientific literature).

The closing pages of the specification (pages 39 to 59) are given over to a series of working examples, along with lengthy passages regarding the various utilities for the method as claimed.

Applicants again point out that they are not claiming compounds. They are claiming a method. What aspect of the method is not described in sufficient detail in the specification as filed?

Applicants explicitly and vehemently traverse the passage at the top of page four of the Final Office Action. There, the Office characterizes the present rejection as follows:

> The question presented by the instant rejection [under §112, first paragraph, written description] is whether Applicant had possession of such a broad genus of 'compounds.'

That is not the proper question at all. The above-quoted passage from the Final Office Action is entirely **irrelevant** to the question at hand. The claims are not directed to compounds. The claims recite a method. All that is required, therefore, is that the specification describe **the method as claimed**, in sufficient detail.

The Final Office Action goes on to conclude (at page 4) that:

> The specification fails to recite a nexus between the genomic DNA and the compounds and also fails to describe any common features or properties of these compound as to indicate that Applicant was in possession of the genus.

What genus? Applicants **are not** claiming a genus of compounds. The claims are drawn to a method. As for a "nexus" between the method and the compounds detected, it is a simple matter of screening the transformed cell line for any quality that is not exhibited by the untransformed host. See, for example, the paragraph spanning pages 29 and 30 of the application as filed.

Claim 2 is directed to a **method** for detecting a compound produced by transforming a host cell to contain isolated genomic DNA. Claim 2 in no way claims the compounds being detected, nor is any knowledge of the compounds required to practice the invention **as claimed**. Any compound produced by the transformed host cell that is not produced by the untransformed host can be detected using the present method. to contain the isolated genomic DNA of step (i) can be detected using the claimed invention. The ultimate nature, identity,

and/or chemical structure of the compound itself is irrelevant for purposes of making and using the **claimed** method. The claims do not require that structure of the compound detected be known or ultimately elucidated. Nor is an inability to do so (to elucidate the structure of the compound detected) fatal to the operability or utility of the claimed invention. The claim is drawn to a **method** of detecting compounds, not determining the structure of the compounds dectected.

Moreover, it is clear from the preamble of Claim 2 that compound produced by a biosynthetic pathway and detected by the positively recited method is not a limitation of Claim 2. The passage "A method for detecting a compound produced by a biosynthetic pathway..." as presented in Claim 2 states the general nature and intended purpose of the invention. It is well settled that if **the body** of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states the purpose or intended use of the invention (rather than any distinct definition of any of the positive limitations of the claims), then the preamble is not considered a limitation (and is of no significance to patentability). *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997): ("Where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation). In short, isolating genomic DNA, inserting the DNA into a replicable vector to clone the DNA, introducing the clones into a host cell, culturing the transformed host cells, and detecting a compound produced by the host cells, are all positive limitations of the claimed invention and therefore must be described in the application. Applicants respectfully submit that each of these steps is described in great detail in the application as filed. However, neither the identity nor the structure of the compounds being detected are positive limitations in Claim 2. Therefore, it is wholly improper for the Office to reject the present method claim based on the nature of the compounds that can be detected using the method.

In other words, Claim 2 is directed to a method for detecting compounds; Claim 2 is not directed to a genus of compounds. Applicants therefore submit that the rejection of Claim

2 under §112, first paragraph (written description) is improper. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 2-30, 32 and 33 under 35 U.S.C. §112, First Paragraph (Enablement):

Claims 32 and 33 were canceled from the case in Applicants' prior response. Therefore, as applied to Claims 32 and 33, this rejection has been rendered moot by cancellation of the claims.

As applied to Claims 2-30, this rejection is respectfully traversed because one does not need any prior knowledge of a compound or the nature of that compound to **detect** its presence in a newly transformed cell.

Examiner states at page 5 of the Office Action that claims 2-30 are not enabling because "to detect the compounds some sort of identification of that compound is required." Applicants strenuously disagree. Quite literally **any** compound can be discovered by countless methods without a whit of knowledge of the structure or identity of the compound detected. In short, Applicants explicitly traverse the Office's conclusion that there is "a very fine distinction" between identification and detection (see page 5 of the Final Office Action, lines 9-10). There is an entire world of difference between detecting a new chemical entity and identifying it.

In their prior response, Applicants pointed out the work of Pierre and Marie Curie, who detected radium before they were able to isolate a sufficient quantity of the material to identify it as a new element. This small bit of history was just one example of a host of suitable examples that amply demonstrate the vast distinction between **detecting** a compound versus **identifying** the compound. Another example involving a very different, non-radioactive compound is the detection and ultimate characterization of penicillin (by Fleming, Chain, and Florey in Great Britain). The penicillin story is particularly enlightening. Fleming first **detected** the compound in 1928, in a culture of staphylococcus that had been contaminated with mold. Despite his clear detection of the compound, and his realization that the compound killed staphylococcus, Fleming could not isolate the compound. Fleming was

also completely and wholly unaware of the structure and chemical nature of penicillin. Fleming had clearly **detected** the compound; he even gave it its name. All in 1928. But Fleming came nowhere close to identifying it. More than a decade passed before Chain and Florey began their efforts to **identify** and characterize penicillin. This work began in 1939, just prior to the outbreak of World War II. See Exhibit A, attached hereto and incorporated herein.

The story of the detection of insulin follows a similar trajectory: Detected in 1921 by Banting and Best in Canada (who had no idea if the compound was a protein or a hormone or some other active agent), the complete amino acid sequence of insulin was not fully elucidated until 1955 (via the work of Frederick Sanger and many others). See Exhibit B, attached hereto and incorporated herein. Exhibit B is a copy of Sanger's Nobel Prize acceptance speech (1958). Reference nos. 13 and 14 present the citations for the two 1955 Sanger et al. papers that reveal the ultimate amino acid sequence for insulin.

In short, there is ample evidence in the prior art that demonstrates that **detecting** a compound is a wholly different matter (and generally far easier matter) than **identifying** the structure of a compound.

Claims 2-30 recite a method of detecting compounds. The nature or identity of the compound detected is irrelevant to the question of enablemetn. The means by which the compound is detected is relevant and a host of suitable means are described in fully enabling detail in the application as filed. The specification is crystal clear about what claims require: detecting a compound in the transformed host that was not present prior to the transformation (see page 3, lines 9-10 of the specification). As noted in the prior section of this response, the application as filed provides a host of information relating to each of the steps positively recited in the claims. Insofar as the Office is requiring some sort of **identification** of the compound detected, a requirement that **is not** part of the pending claims, this rejection under the enablement provision of §112, first paragraph is clearly improper.

Regarding the assay to be used and expected results, Applicants submit that the specification as filed contains a wealth of information, including extensive citations to the prior art, for various methods to detect compounds produced by the transformed host cells.

Again, the Office's attention is directed to pages 29-39 of the specification for an extensive discussion of various detection methods: Methods specifically addressed for detecting new compounds produced by the transformed host cells include classical fractionation techniques (*e.g.*, chromatographic separation), solvent fractionation, photometric techniques (*e.g.*, fluorescence or phosphorescence). The specification also describes assaying the transformed cells by contacting a test sample from the transformed cells with a test cell (see page 31 of the specification). The specification goes on to state that the assay can be arranged to detect, for example, a phenotypic change in the test cell, such as a change in the transcriptional or translational rate or splicing pattern of a gene; the stability of a protein; the phosphorylation, prenylation, methylation, glycosylation, or other post-translational modification of a protein, nucleic acid, or lipid; the production of 2nd messengers, such as cAMP, inositol phosphates, and the like. The specification explicitly indicates that such effects can be measured directly (such as by isolating and studying a particular component of the test cell) or indirectly (such as by the expression of a reporter gene, or via cytotoxic or cytostatic activity imparted to the test cell.)

Pages 31 and 32 of the specification teach very specific assays that can be used to detect compounds, *i.e.*, detecting compound by measuring changes in GTPase activity of cAMP production between the unmodified host cells and the transformed host cells; using the activity of phospholipase C as a means to compare the unmodified host cells to the transformed host cells; using the activity of phospholipase C as a means to detect new compounds produced by the transformed host cells; and assaying for changes to cellular phosphorylation. Further, the MAP kinase pathway is explicitly offered as an exemplary pathway that can be used as an assay.

Page 33 of the specification discusses using a substrate that, when converted to a particular product, produces a detectable change in the optical characteristics of the test cell; *e.g.*, one of the substrate or its resulting product are chromogenically or fluorogenically active. Thus, a new compound produced by the transformed cells that acts upon the substrate can be detected by measuring an increase or decrease in, for example, the fluorescent signal generated by the added substrate. No knowledge whatsoever of the compound detected is

required in order actually to detect a new compound not produced by the untransformed host. Further, several suitable substrates are mentioned, along with five (5) prior art patents and one (1) prior art paper that describe these types of assays. For instance, page 33 discusses detecting the compound by using enzymes or fluorescent probes whose activities are dependent upon the concentration of a second messenger compound (potentially produced by the transformed cells).

Pages 35-36 of the specification discuss using reporter genes and transcriptional regulatory elements to detect compounds produced by the transformed host cells that are not produced by the unmodified host cells. Page 37 of the specification teaches the use of cell-free detection systems for measuring the formation of a protein complex as a primary screen to detect new compounds as well as the use of an interactive trap assay to detect compounds produced by the transformed cells not produced by the unmodified cells. Page 38 discusses enzyme assays to detect compounds produced by the transformed host cells. Finally, page 40 provides a clear, specific, working example of taking conditioned culture medium from the transformed cells and testing it for nematicidal activity against *C. elegans*, and then following up with insecticidal activity against a variety of insects.

In short, the specification as filed clearly teaches one of skill in the art what to look for - a compound that was not present prior to transformation. Further, the specification as filed clearly teaches one of skill in the art a multitude of assays to use to detect the compound. Claims 2-30 do **not** require that the compound be identified; the claims require only that the presence of the compound be detected. Therefore, Applicants respectfully submit that, contrary to the assertion advanced by the Office, the compounds do **not** need to be identified in any way, shape or form, to be "detected."

In light of the above remarks, Applicants respectfully submit that the rejection of claims 2-30 under 35 U.S.C. §112, first paragraph (enablement) is improper. Withdrawal of the rejection is requested.

Rejection of Claims 2-6, 8-30, 41 and 46-48 under 35 U.S.C. §112, First Paragraph (Written Description):

Applicants submit this rejection has been overcome by appropriate amendment to the claims. Independent claims 2 and 41 have been amended to recite the negative limitation "without an intervening step of culturing cells from the source." Verbatim support for this limitation can be found in the specification as filed at page 13, lines 12-13 (as was acknowledged by the Office in the Final Office Action at page 7). Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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